

Manuscript Number: JVAC-D-13-01748R1

Title: Reply: Letter to the Editor, Cochrane Rearranged

### Authors' reply

We appreciate the response of Osterholm and colleagues to our re-analysis of the clinical evidence of influenza vaccine effectiveness in elderly adults, accumulated during the past 40 years. Osterholm et al. have raised four objections against our main conclusion that vaccination reduces influenza infection and influenza-related disease in elderly adults. In our opinion, these objections do not invalidate our conclusion.

#### 1. Antibody ceiling bias

As stated by Osterholm et al, some studies did indeed rely on antibody titre rises in pairs of pre- and post-season sera to detect influenza infections, in particular the randomised controlled trial of Govaert et al. [1] from the early 1990s when advanced detection methods, like the real-time polymerase chain reaction (rtPCR), were not yet available. An antibody ceiling bias may have affected Govaert et al's estimation of serological vaccine efficacy, but has likely not entirely invalidated it. More importantly, the protection from influenza-like illness assessed clinically without serology, was also significant and pointed in the same direction as the serological estimate.

#### 2. Biological vaccine efficacy and cut-off level for seroprotection

We agree with the cited statement of the Food and Drug Administration, and therefore we have not defined biological vaccine efficacy by any cut-off HI antibody titre. We have also found that the association between protection and a specific antibody cut-off point is poor [2]. Pre-season HI antibody and protection are strongly connected in a curvilinear manner: the higher the antibody titre, the lower the chance of infection [3]. Estimation of protection from antibody titres is possible if the entire protection curve (rather than a single cut-off point) is considered. In our Supporting Material 2, last paragraph, we have covered this subject. So, this objection must be a misunderstanding. Incidentally, the literature retrieval performed by the Cochrane Collaboration (and on which we base our entire re-analysis) already excluded pure antibody vaccination studies (those reporting pre- and post-vaccination titres without clinical follow-up). Consequently, the data used in our article consists entirely of follow-up outcomes.

#### 3. All-cause mortality studies

We could not agree more with Osterholm et al. that vaccine effectiveness estimated from observational studies of all-cause mortality are likely to be heavily biased. We found a mean effectiveness of 48% in the studies reviewed, contrasting sharply with the average effectiveness figure of 4.6% from the exceptional study by Fireman et al. [4]; we explain the discrepancy as a healthy user effect, according to Simonson et al. [5]. Consequently, we excluded all-cause mortality studies from our main analysis. What Osterholm et al. are presenting as disagreement between their and our position, is in fact, from our perspective, a complete agreement.

#### 4. Studies applying the test-negative design

The test-negative design has increasingly been used during the last years and is very promising, indeed. The main theoretical problem of this design is the same as in all observational studies: the exposure risk may not be the same in vaccinated and unvaccinated persons [6] potentially leading to a large variation of the effectiveness estimates between places and seasons. Single study results from a limited number of seasons, like the 27% and 9% point estimates mentioned by Osterholm et al., should therefore be interpreted with caution, and cannot easily be compared with our averages and ranges based on 40 years of observations across numerous studies. We refer to Figure 2 of our article: note how large the ranges of the three described effectiveness measures are, compatible with large inter-season variation. The point estimates quoted by Osterholm et al. are situated within these ranges. Only the entirety of many studies from many years reveals the complete pattern of vaccine effectiveness and allows the estimation of an average biological vaccine efficacy.

Thus, we feel that the four objections of Osterholm et al. do not challenge, let alone disprove, our main conclusion that influenza vaccination significantly reduces the risks of infection and disease in elderly adults, even with the imperfect formulations of the inactivated vaccines in common usage during the last four decades. New generation vaccines, specifically developed for elderly adults, should further improve protection. We support policies to vaccinate elderly people against influenza.

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